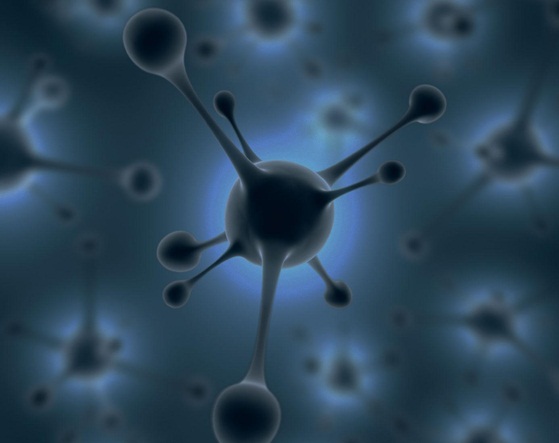
*The Oxygen Paradox*

# The Oxygen–Antioxidant Paradox November 17, 2008 By Dr. Hugh Ross <http://www.reasons.org/articles/the-oxygen-antioxidant-paradox>



The oxygen-antioxidant paradox seriously challenges all naturalistic models attempting to explain the history of life on Earth. Consequently, confirming its validity would do much to establish a biblical creation model. The results of a recent test have provided that validity.

Advanced life requires the efficient processing of energy to perform work. Only the oxidation of carbohydrates, starches, and fats can deliver the necessary efficiency. However, the presence of oxygen within cells forms free radicals (atoms or groups of atoms with odd numbers of electrons). Once formed, these free radicals can launch chain reactions that quickly damage DNA, membranes, and proteins, resulting in either severely damaging or killing the cells.

In order to prevent free radical damage, the cells of advanced life must possess a system of antioxidants. Antioxidants are molecules that safely interact with free radicals inside the cell to stop the chain reactions before any significant damage can occur.

This results in the oxygen-antioxidant paradox. Unless the capacity to oxidize carbs, starches, and fats and a comprehensive system of antioxidant defenses develop at the same time and place in a symbiotically integrated manner advanced life is impossible. In other words, a fully functional antioxidant defense system must be in place before the launch of any oxidative metabolic life.

The challenge for naturalists is to explain, without the agency of a supernatural, super-intelligent Creator, why a complex, comprehensive antioxidant defense system would spontaneously evolve before any need for such a system existed. Naturalists must also explain why oxidative metabolic life would spontaneously evolve before an intact and fully operational antioxidant defense system exists, or more challenging yet, why both would simultaneously and instantly evolve at the same location.

Underscoring the dilemma for naturalists is an [experiment performed by a team of ten scientists at Lyon College](http://www.liebertonline.com/doi/abs/10.1089/ast.2008.1262).1 The team compared the growth rate of a wild strain of the cyanobacterium, *Synechococcus*, against two different mutant strains in two different environments: the first in a zero-oxygen environment and the second in an oxygen-rich environment. Each mutant strain manifested a different crippling of the antioxidant defense systems. The mutant strains had lower growth rates than the wild strain under both oxygen-rich and zero-oxygen conditions. Such a result confirmed that the antioxidant defense systems must have been fully present and operational before the appearance of oxygenic photosynthesis. Thus, the experimental outcome confirms the severe challenge that the origin of oxygenic photosynthesis presents to any naturalistic model for life.

Subjects: Life on Other Planets, Prebiotic Chemistry, Primordial Soup

# Dr. Hugh Ross

Reasons to Believe emerged from my passion to research, develop, and proclaim the most powerful new reasons to believe in Christ as Creator, Lord, and Savior and to use those new reasons to reach people for Christ. [Read more about Dr. Hugh Ross.](http://www.reasons.org/about/who-we-are/hugh-ross)

#### References: David Thomas et al., “A Test of the Oxygen Paradox Using Antioxidant-Deficient Cyanobacteria,”Astrobiology 8 (April 2008): 471.

[*http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762*](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762)

*“By denying scientific principles, one may maintain any paradox.” Galileo Galilei*

One of the life’s paradoxes is the fact that the molecule supporting aerobic life-oxygen-is not just essential for the energetic metabolism and for respiration, but almost equally involved in the ethiopatogenesis of numerous diseases and degenerative states due to oxygen-based reactive species called free radicals (FR). Nature has selected and included, in an evolutionary manner, in the composition of living bodies, reactions generating FR with multiple roles: functional, intercellular communicational or destructive, cytolitic, etc. At molecular level the main target of the free radical is the sulphurhydril free or protein groups, while at cellular level the main target are cellular membranes. FR occurs in the body, as the result of endogenous metabolic activity or of the local assimilation of some chemical pollutants at cellular level or at the level of several tissues, simultaneously or gradually. Due to their high reactivity, FR has been found responsible for many noxious effects on the living body. Oxidative stress is defined as an exaggerated production of oxygenated FR, accompanied by a dislocation of antioxidation agents. We cannot live without oxygen, since it is essential in the functioning of energy-producing cells. A body transforms and eliminates oxygen (CO2) properly almost entirely (98%) [[1](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#1)]. Unfortunately, the rest is at the origin of some “hyper-reactive” species called FR (is oxidated derivatives of the electron deficit, unstable oxygen molecule, that cause dysfunctions of all body cells). The volume of oxygen contained by a single inspiration produces a billion FR. Reactive oxygen species (ROS) are at the origin of chain reactions, such a radical, unstable as a result of the electron deficit, captures the missing electron from a “foreign” molecule that becomes, in its turn, an unstable radical, and the process goes on and on [[2](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#2)]. Such reactions occur quasi-instantaneously, at speeds of the order of billions/second, until the deficit electron is formed by a neuter, stable molecule, but whose physiological function is altered. It results in lesions of the nucleic acids involved in cell division or in protein synthesis that become incapable of transporting the oxygen necessary to the metabolism [[3](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#3)]. The activity of FR was described as a sort of “*inner radiation*” attacking and damaging cells/tissues, resulting in different symptoms usually attributed to ageing [[4](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#4)]. The damaging effects of normally producing ROS in the body are under control by specialised removal enzymes. Both diseases and adaptations to the environment are linked to the alteration of the body chemical metabolism characterised by the transition from heterolithic (2 electrons are attracted/released) to the increase of homolithic processes (1 electron is transited). Homolithic reactions produce radicals that can react, damaging cell compartments, tissues, and organisms. These reactions that generate ROS reach equilibrium through the inner increase of oxidative processes or by the presence of antioxidant compounds [[5](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#5)]. The main actions of ROS in a biological system are: oxidation of unsaturated fatty acids in the cell membrane, oxidation of aminoacids in proteins, depolymerisation of hialuric acid, oxidation of DNA oxidative products, modulation of the nucleotide cyclase activity, modulation of prostaglandin activity and synthesis, etc [[6](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#6)-[8](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#8)]. The current concepts of ROS signalling can be grouped into two action mechanisms: − *Alterations of intracellular redox state:* Compared to the extra-cell environment, cytoplasm is normally maintained in reducing conditions (accompanied by the buffer redox capacity of intra-cell thiol such as GSH and TRX-thioredoxin). These thiol systems oppose intra-cell oxidative stress reducing H2O2, lipid superoxides and peroxides (catalysed by peroxidases). − *Protein oxidative changes:* ROS can alter the structure and function of proteins, changing the rest of amino acids, inducing protein dimerisation and interacting with other metal complexes (Fe-S). Oxidative changes of amino acids in the protein functional domain can involve several pathways [[9](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#9)]. The target cell components of free radical action include lipids (low-density lipoproteins), macromolecules with complex structure, proteins and DNA. In order to minimise the negative effects of ROS, organisms are endowed with very efficient antioxidant defence system [[10](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#10)]. In the presence of oxidative stress, i.e. of a positive oxidative balance the most vulnerable system of a body is the central nervous system. Health state analysis has thus shifted from cell level to molecular level (molecular biology-ROS) and to atomic level (atomic physics-electrons) [[11](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#11)-[13](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#13)]. This is the biochemical and biophysical context in which the action of anti-oxidative compounds, taking into account that oxidative stress, is responsible for about 80-90% of chronic-degenerative diseases associated to ageing. The ageing is not a chronological process caused by the passage of time, but rather a biological process determined by the speed that ROS are assimilated by the body, destroying cells, attacking tissues, and affecting vital functions [[14](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#14)-[17](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#17)]. ROS produced by one’s own body play a role in the cell defence system, destroying bacteria and viruses, decomposing chemical pollutants, and neutralising toxins [[18](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#18)]. Living organisms and, particularly, the *encephalus*, are very sensitive to the damage produced by FR [19]. Most probably, this is due to the following factors: electron-rich neuronal biomolecules (histidine, tryptophan, etc.) recognise the oxygen radical, an electrophilous ROS (it alters histaminergic and serotoninergic systems); neuronal membranes are rich in polyunsaturated fatty acids (privileged molecular substratum of ROS); neuronal mitochondria are represented in large numbers (mitochondria are the cell core of FR); neurons are easily subjected to dedifferentiation as a result of the attack by ROS on the DNA (they lose their own genetic specialisation or differentiation and turn into neuter cells, with no specific function); neuronal oxygen is certainly present since the brain, unlike other organs and tissues, has an overall aerobic energetic metabolism [[20](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#20)-[24](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#24)]. At the brain level, there are small amounts of enzymatic and non-enzymatic antioxidants. Vitamin C is an exception, as it has, at brain level, a concentration 50 times higher than in any other part of the organism [[25](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#25)]. This is the key-substance for the protection of the central nervous system against FR. Neurons are “perennial cells” and the cumulated lesions produced by ROS on the different cell structures could, in time, degrade quantitatively and qualitatively, the neurotransmission functions and result in behavioural changes [[26](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#26)]. The postulate of the ageing theory is based on the reactions of FR involved in the changes caused by ageing. The changes are associated with the environment, with diseases, and with the intrinsic ageing process. This theory is based on the chemical nature of the reactions of ROS and on their omnipresence. The most reactive of all ROS is hydroxyl, which reacts with deoxiribose and the bases of the DNA. As a result of the postulate of the ageing theory, we can draw two conclusions on the relationship between the deterioration of the DNA and maximum life span. The increase agents/processes of the rate of deterioration of the DNA or the decrease of DNA recovery can speed up the ageing process. Thus, decreasing life span and apparent deterioration speed, we can decrease proportionally the speed of the specific metabolism (the energetic nutritional supplement). ROS are considered factors that cause cell dedifferentiation since they react with chromatin, they change the bases of the DNA, and they cause ruptures of the chain [[27](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#27)-[29](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#29)]; they induce chromosomal aberrations and a long life in the species with a low rate of accumulation of chromosomal aberrations; long life species have a low rate of accumulation of age pigments, lipofuscine, because ageing rate is proportional with metabolic rate for many different species [[30](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#30)- [32](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#32)]. The factor determining the increase of the intensity of free radical formation is oxygen activation. Due to the presence of this element not only in the atmosphere but also in almost all the substances in the body, the interaction of FR with oxygen is inevitable [[33](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#33)]. They attack the existing pro-oxidants (substances/ions) for which the ROS have an affinity. ROS occur in certain reactions of oxidoreduction resulting in structural alterations, in most cases with the alteration of the biological function (it becomes more hydrosoluble or it intervenes in another chain of metabolic reactions) [[34](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#34)]. The human body has natural antioxidants; they make up a complex of enzymes, vitamins, metals, and aminoacids functioning in association at two levels: it identifies ROS and guides them towards antioxidant molecules that neutralise them and re-develop them again. Antioxidants donate or receive a supplementary electron to neutralise ROS and to put an end to the oxidation cascade of oxidation [[35](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#35)-[37](http://www.omicsonline.org/the-oxygen-paradox-2153-0645.1000e104.php?aid=3762#37)]. ROS forms at mitochondrial level, during the respiratory chain, as well as a result of enzymatic reactions. The speed of formation of ROS depends on the speed of use of the oxygen, and it is directly proportional with the number of mitochondria in the cell. The importance of FR can only be understood if we know well their role. Evolutively, nature has selected and included in the human body, reactions generating ROS with multiple roles: functional, intracellular communication, or destructive, cytolitic. If, at molecular level, the main target of the ROS is the free or protein groups SH, at cellular level, the major goal is cell membranes. ROS can be formed in the body as a result of endogenous metabolic activity or of the assimilation of chemical pollutants-locally, at cell level, or in several tissues, simultaneously or gradually. Because of their high reactivity, ROS has been incriminated in many noxious body actions. As a conclusion, ROS and oxidative stress play an important role in the induction of dysfunctions at cell level and of different diseases at body level. The balance between the antioxidant action of ROS and the level of antioxidants in a body is essential for life and it characterizes the capacity of resistance and adaptation of a living body. *“A perfection of means, and confusion of aims, seems to be our main problem.” Albert Einstein* References

1. Matzinger P (2007)[Friendly and dangerous signals: is the tissue in control? Nat Immunol 8: 11-13.](http://www.ncbi.nlm.nih.gov/pubmed/17179963)
2. Floyd RA (2009)[Serendipitous findings while researching oxygen free radicals. Free Radic Biol Med 46: 1004-1013.](http://www.ncbi.nlm.nih.gov/pubmed/19439210)
3. Rizzo AM, Berselli P, Zava S, Montorfano G, Negroni M, et al. (2010)[Endogenous antioxidants and radical scavengers. Adv Exp Med Biol 698: 52-67.](http://www.ncbi.nlm.nih.gov/pubmed/21520703)
4. Williams HE, Claybourn M, Green AR (2007)[Investigating the free radical trapping ability of NXY-059, S-PBN and PBN. Free Radic Res 41: 1047-1052.](http://www.ncbi.nlm.nih.gov/pubmed/17729123)
5. Gutierrez J, Ballinger SW, Darley-Usmar VM, Lander A (2006)[Free radicals, mitochondria, and oxidized lipids: the emerging role in signal transduction in vascular cells. Circ Res 99: 924-932.](http://www.ncbi.nlm.nih.gov/pubmed/17068300)
6. Hathwar SC, Bijinu B, Rai AK, Narayan B (2011)[Simultaneous recovery of lipids and proteins by enzymatic hydrolysis of fish industry waste using different commercial proteases. Appl Biochem Biotechnol 164: 115-124.](http://www.ncbi.nlm.nih.gov/pubmed/21057982)
7. Gustafsson ÅB, Gottlieb RA (2008)[Heart mitochondria: gates of life and death. Cardiovasc Res 77: 334-343.](http://www.ncbi.nlm.nih.gov/pubmed/18006487)
8. Cynshi O, Tamura K, Niki E (2010)[Design, synthesis, and action of antiatherogenic antioxidants. Methods Mol Biol 610: 91-107.](http://www.ncbi.nlm.nih.gov/pubmed/20013174)
9. Ozcan ME, Gulec M, Ozerol E, Polat R, Akyol O (2004)[Antioxidant enzyme activities and oxidative stress in affective disorders. Int Clin Psychopharmacol 19: 89-95.](http://www.ncbi.nlm.nih.gov/pubmed/15076017)
10. Jankun J (2011)[Protein-based nanotechnology: Antibody conjugated with photosensitizer in targeted anticancer photoimmunotherapy. Int J Oncol 39: 949-953.](http://www.ncbi.nlm.nih.gov/pubmed/21725592)
11. Chander V, Chopra K (2005)[Molsidomine, a nitric oxide donor and L-arginine protects against rhabdomyolysis-induced myoglobinuric acute renal failure. Biochim Biophys Acta 1723: 208-214.](http://www.ncbi.nlm.nih.gov/pubmed/15777642)
12. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M (2006)[Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 160: 1-40.](http://www.ncbi.nlm.nih.gov/pubmed/16430879)
13. Pickrell AM, Fukui H, Moraes CT (2009)[The role of cytochrome c oxidase deficiency in ROS and amyloid plaque formation. J Bioenerg Biomembr 41: 453-456.](http://www.ncbi.nlm.nih.gov/pubmed/19795195)
14. Sari I, Cetin A, Kaynar L, Saraymen R, Hacioglu SK, et al. (2008)[Disturbance of pro-oxidative/antioxidative balance in allogeneic peripheral blood stem cell transplantation. Ann Clin Lab Sci 38: 120-125.](http://www.ncbi.nlm.nih.gov/pubmed/18469356)
15. Surapaneni KM, Venkataramana G (2007)[Status of lipid peroxidation, glutathione, ascorbic acid, vitamin E and antioxidant enzymes in patients with osteoarthritis. Indian J Med Sci 61: 9-14.](http://www.ncbi.nlm.nih.gov/pubmed/17197733)
16. Takabe W, Li R, Ai L, Yu F, Berliner JA, et al. (2010)[Oxidized Low-Density Lipoprotein-Activated C-Jun NH2-Terminal Kinase Regulates Manganese Superoxide Dismutase Ubiquitination. Implication for Mitochondrial Redox Status and Apoptosis. Arterioscler Thromb Vasc Biol 30: 436-441.](http://www.ncbi.nlm.nih.gov/pubmed/20139358)
17. Horvath G, Brubel R, Kovacs K, Reglodi D, Opper B, et al. (2011)[Effects of PACAP on Oxidative Stress-Induced Cell Death in Rat Kidney and Human Hepatocyte Cells. J Mol Neurosci 43: 67-75.](http://www.ncbi.nlm.nih.gov/pubmed/20676802)
18. Kaynar H, Meral M, Turhan H, Keles M, Celik G, et al. (2005)[Glutathione peroxidase, glutathione-S-transferase, catalase, xanthine oxidase, Cu-Zn superoxide dismutase activities, total glutathione, nitric oxide, and malondialdehyde levels in erythrocytes of patients with small cell and non-small cell lung cancer. Cancer Lett 227: 133-139.](http://www.ncbi.nlm.nih.gov/pubmed/16112416)
19. Waris G, Ahsan H (2006)[Reactive oxygen species: role in the development of cancer and various chronic conditions. J Carcinog 5: 14.](http://www.ncbi.nlm.nih.gov/pubmed/16689993)
20. Orient A, Donko A, Szabo A, Leto TL, Geiszt M (2007)[Novel sources of reactive oxygen species in the human body. Nephrol Dial Transplant 22: 1281-1288.](http://www.ncbi.nlm.nih.gov/pubmed/17347280)
21. Budisavljevic MN, Hodge L, Barber K, Fulmer JR, Durazo-Arvizu RA, et al. (2003)[Oxidative stress in the pathogenesis of experimental mesangial proliferative glomerulonephritis. Am J Physiol Renal Physiol 285: 1138-1148.](http://www.ncbi.nlm.nih.gov/pubmed/14600028)
22. Haussinger D, Schliess F (2008)[Pathogenetic mechanisms of hepatic encephalopathy. Gut 57: 1156-1165.](http://www.ncbi.nlm.nih.gov/pubmed/18628377)
23. Montoliu C, Cauli O, Montoliu C, Rodrigo R, Llansola M, et al. (2009)[Mechanisms of cognitive alterations in hyperammonemia and hepatic encephalopathy: Therapeutical implications. Neurochem Int 55: 106-112.](http://www.ncbi.nlm.nih.gov/pubmed/19428813)
24. Pirker A, Kramer L, Voller B, Loader B, Auff E, et al. (2011)[Type of Edema in Posterior Reversible Encephalopathy Syndrome Depends on Serum Albumin Levels: An MR Imaging Study in 28 Patients. AJNR Am J Neuroradiol 32: 527-531.](http://www.ncbi.nlm.nih.gov/pubmed/21252042)
25. Ajith TA, Usha S, Nivitha V (2007)[Ascorbic acid and alpha-tocopherol protect anticancer drug cisplatin induced nephrotoxicity in mice: a comparative study. Clin Chim Acta 375: 82-86.](http://www.ncbi.nlm.nih.gov/pubmed/16889761)
26. Lemberg A, Fernandez MA (2009)[Hepatic encephalopathy, ammonia, glutamate, glutamine and oxidative stress. Ann Hepatol 8: 95-102.](http://www.ncbi.nlm.nih.gov/pubmed/19502650)
27. O'Hare F, Watson R, O'Neill A, Donoghue V, O'Donnell C, et al. (2011)[Significantly Elevated Systemic Neutrophil Reactive Oxygen Intermediates are Associated with Severe Neonatal Encephalopathy. Pediatr Res 70: 684-684.](http://www.nature.com/pr/journal/v70/n5s/abs/pr2011909a.html)
28. Wang D, Chen Y, Chabrashvili T, Aslam S, Borrego Conde LJ, et al. (2003)[Role of oxidative stress in endothelial dysfunction and enhanced responses to angiotensin II of afferent arterioles from rabbits infused with angiotensin II. J Am Soc Nephrol 14: 2783-2789.](http://www.ncbi.nlm.nih.gov/pubmed/14569088)
29. Shibata S, Nagase M, Yoshida S, Kawachi H, Fujita T (2007)[Podocyte as the target for aldosterone: roles of oxidative stress and Sgk1. Hypertension 49: 355-364.](http://www.ncbi.nlm.nih.gov/pubmed/17200434)
30. Sachse A, Wolf G (2007)[Angiotensin II-induced reactive oxygen species and the kidney. J Am Soc Nephrol 18: 2439-2446.](http://www.ncbi.nlm.nih.gov/pubmed/17687073)
31. Lambeth JD (2007)[Nox enzymes, ROS, and chronic disease: an example of antagonistic pleiotropy. Free Radic Biol Med 43: 332-347.](http://www.ncbi.nlm.nih.gov/pubmed/17602948)
32. Bhatti F, Mankhey RW, Asico L, Quinn MT, Welch WJ, et al. (2005)[Mechanisms of antioxidant and pro-oxidant effects of alphalipoic acid in the diabetic and nondiabetic kidney. Kidney Int 67: 1371-1380.](http://www.ncbi.nlm.nih.gov/pubmed/15780089)
33. Bakris GL (2007)[Pharmacological augmentation of endothelium-derived nitric oxide synthesis. J Manag Care Pharm. 13: 9-12.](http://www.ncbi.nlm.nih.gov/pubmed/17605505)
34. Fialkow L, Wang Y, Downey GP (2007)[Reactive oxygen and nitrogen species as signaling molecules regulating neutrophil function. Free Radic Biol Med 42: 153-164.](http://www.ncbi.nlm.nih.gov/pubmed/17189821)
35. Angermuller S, Islinger M, Volkl A (2009)[Peroxisomes and reactive oxygen species, a lasting challenge. Histochem Cell Biol 131: 459-463.](http://www.ncbi.nlm.nih.gov/pubmed/19224237)
36. Bonekamp NA, Volkl A, Fahimi HD, Schrader M (2009)[Reactive oxygen species and peroxisomes: struggling for balance. Biofactors 35: 346-355.](http://www.ncbi.nlm.nih.gov/pubmed/19459143)
37. Seo KW, Kim KB, Kim YJ, Choi JY, Lee KT, et al. (2004)[Comparison of oxidative stress and changes of xenobiotic metabolizing enzymes induced by phthalates in rats. Food Chem Toxicol 42: 107-114.](http://www.ncbi.nlm.nih.gov/pubmed/14630134)

**Oxidative stress: the paradox of aerobic life.**

[Davies KJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Davies%20KJ%5BAuthor%5D&cauthor=true&cauthor_uid=8660387)1. <http://www.ncbi.nlm.nih.gov/pubmed/8660387> **Abstract**

The paradox of aerobic life, or the 'Oxygen Paradox', is that higher eukaryotic aerobic organisms cannot exist without oxygen, yet oxygen is inherently dangerous to their existence. This 'dark side' of oxygen relates directly to the fact that each oxygen atom has one unpaired electron in its outer valence shell, and molecular oxygen has two unpaired electrons. Thus atomic oxygen is a free radical and molecular oxygen is a (free) bi-radical. Concerted tetravalent reduction of oxygen by the mitochondrial electron-transport chain, to produce water, is considered to be a relatively safe process; however, the univalent reduction of oxygen generates reactive intermediates. The reductive environment of the cellular milieu provides ample opportunities for oxygen to undergo unscheduled univalent reduction. Thus the superoxide anion radical, hydrogen peroxide and the extremely reactive hydroxyl radical are common products of life in an aerobic environment, and these agents appear to be responsible for oxygen toxicity. To survive in such an unfriendly oxygen environment, living organisms generate--or garner from their surroundings--a variety of water- and lipid-soluble antioxidant compounds. Additionally, a series of antioxidant enzymes, whose role is to intercept and inactivate reactive oxygen intermediates, is synthesized by all known aerobic organisms. Although extremely important, the antioxidant enzymes and compounds are not completely effective in preventing oxidative damage. To deal with the damage that does still occur, a series of damage removal/repair enzymes, for proteins, lipids and DNA, is synthesized. Finally, since oxidative stress levels may vary from time to time, organisms are able to adapt to such fluctuating stresses by inducing the synthesis of antioxidant enzymes and damage removal/repair enzymes. In a perfect world the story would end here; unfortunately, biology is seldom so precise. The reality appears to be that, despite the valiant antioxidant and repair mechanisms described above, oxidative damage remains an inescapable outcome of aerobic existence. In recent years oxidative stress has been implicated in a wide variety of degenerative processes, diseases and syndromes, including the following: mutagenesis, cell transformation and cancer; atherosclerosis, arteriosclerosis, heart attacks, strokes and ischaemia/reperfusion injury; chronic inflammatory diseases, such as rheumatoid arthritis, lupus erythematosus and psoriatic arthritis; acute inflammatory problems, such as wound healing; photo-oxidative stresses to the eye, such as cataract; central-nervous-system disorders, such as certain forms of familial amyotrophic lateral sclerosis, certain glutathione peroxidase-linked adolescent seizures, Parkinson's disease and Alzheimer's dementia; and a wide variety of age-related disorders, perhaps even including factors underlying the aging process itself. Some of these oxidation-linked diseases or disorders can be exacerbated, perhaps even initiated, by numerous environmental pro-oxidants and/or pro-oxidant drugs and foods. Alternatively, compounds found in certain foods may be able to significantly bolster biological resistance against oxidants. Currently, great interest centres on the possible protective value of a wide variety of plant-derived antioxidant compounds, particularly those from fruits and vegetables.

# Oxygen in the Evolution of Complex Life and the Price We Pay <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/> [Victor J. Thannickal](http://www.ncbi.nlm.nih.gov/pubmed/?term=Thannickal%20VJ%5Bauth%5D)1

[Author information ►](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/) [Article notes ►](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/) [Copyright and License information ►](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/)

This article has been [cited by](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/citedby/) other articles in PMC.

Aerobic organisms use molecular oxygen (dioxygen; O2) to generate chemical energy in the form of adenine triphosphate (ATP). Energy transforms cellular structure to function, a defining property of life. Due to its favorable thermodynamic properties, O2 appears to have been selected during biological evolution to serve as the terminal electron acceptor in the reduction of carbon-based fuels to generate ATP by oxidative phosphorylation. That O2 is essential to sustain human life is perhaps best illustrated during an acute cardiopulmonary arrest—commonly referred to as “code blue” on the medical wards. Indeed, the “A-B-Cs” of basic life support is to ensure gas-exchange via the lungs and O2 delivery to internal organs: “A” for airway, “B” for breathing, and “C” for circulation. A less well appreciated role of O2 is in the evolution of organismal size, multicellularity, and biological complexity. An understanding of the key role of O2 in the evolution of complex life and mammalian physiology may provide novel insights of O2, and its metabolites (reactive oxygen species), in the pathophysiology of diseases that affect the lung.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/)

## O2 AND METAZOAN EVOLUTION

Multiple lines of evidence from evolutionary biology ([1](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib1), [2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib2)), geochemistry ([3](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib3)), and systems biology ([4](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib4)) build a compelling case for a central role of O2 in the evolution of complex multicellular life on earth ([5](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib5), [6](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib6)). The oldest life forms are estimated to have been present over 3.7 billion years (Gyr) ago ([7](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib7)). In the relative absence of O2 and under the strong reducing conditions that existed on the primordial earth's surface, early unicellular life forms relied on metabolic pathways that used electron acceptors such as CO2 and SO4. Between about 2.5 and 2.2 Gyr ago, however, the earth's atmospheric concentration of O2 rose significantly ([3](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib3)). This rise in atmospheric O2 is thought to have been due to biological and geological factors that led to an increase in O2 production relative to its consumption. Biological processes, most notably the emergence of cyanobacteria capable of oxygenic photosynthesis ([8](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib8)), were an important source of O2 production during this early period. Geological events such as the burial of organic carbon ([9](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib9)) and a shift from submarine to subaerial volcanism ([10](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib10)) accounted for decreased O2 consumption.

The availability of O2 was a major coup for early life forms, since it allowed for the use of energy-efficient metabolic pathways. O2 is well suited to serve as an electron acceptor in the oxidation of carbon-based fuels for several reasons. First, the reduction of O2 provides the largest free energy release per electron transfer, with the exception of fluorine. Second, unlike fluorine, ground state triplet O2 is a diradical with its outer electrons in parallel spin, allowing for its greater stability and consequent accumulation in the earth's atmosphere. Third, aerobic metabolism yields at least 4-fold more energy per molecule of glucose oxidized than the most efficient anaerobic pathways. Fourth, ability of O2 to diffuse across biological membranes and to bind heme moieties in proteins (e.g., hemoglobin and cytochromes) facilitates O2 delivery to systemic organs and mitochondrial electron transfer functions. Finally, the biochemical symmetry of oxygenic photosynthesis and aerobic respiration (H2O → O2 → H2O cycle) maintains homeostasis within our planetary biosphere.

Increasing complexity in metazoan evolution has been linked to rising atmospheric O2 levels and the ability to use O2 to generate energy more efficiently ([11](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib11)). The evolution of the lung and circulatory system would have been critical for the transport of O2 to internal tissues/organs in larger, more complex metazoans, otherwise limited by the diffusibility of O2 across multiple cell layers. Complexity in organismal structure and function has been linked with the number of differentiated cell types and overall size of adult organisms ([12](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib12)). Estimates of the maximum number of cell types of common ancestors, combined with divergence times, showed an increase from 2 to approximately 10 cell types between 2.5 and 2.0 Gyr ago, and from 10 to 50 cell types between 1.5 and 1.0 Gyr ago ([11](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib11)) ([Figure 1](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig1/)). The most prolific increase in speciation, however, occurred during the “Cambrian explosion,” approximately 540 million years ago. A second major rise in O2concentration is thought to have been a critical factor ([13](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib13)), among other events such as mass extinctions ([14](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib14)), that created the “perfect storm” for this evolutionary diversification. A larger increase in O2 concentration occurred just before ∼ 300 million years ago, and this period was associated with the emergence of reptile and insect gigantism; the subsequent drop in O2 concentration during the Permian-Triassic period (∼ 260–245 million years ago) appears to have led to their extinction ([15](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib15)). The rise of O2 levels from approximately 10% (205 million years ago) to the current approximately 21% corresponds with vertebrate evolution and emergence of its key features: endothermy, placentation, and body size (humans are estimated to have > 200 different “cell types”) ([1](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib1)) ([Figure 1](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig1/)).

[Figure 1.](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig1/)

[**Figure 1.**](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig1/)

Temporal relationships between estimated atmospheric O2concentrations, evolutionary diversification, and biological complexity. The first period of rapid O2 accumulation occurred approximately 2.3 billion years (Gyr) ago (the “great oxidation **...**

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/)

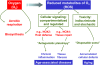
## O2 IN CELLULAR PHYSIOLOGY: MORE THAN AEROBIC METABOLISM

The physiologic role of O2 in metazoan species is not limited to mitochondrial respiration. Recent biochemical networks analysis demonstrate that O2 is among the most-used compounds in a myriad of metabolic and biosynthetic pathways, superseding even adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NAD+) ([4](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib4)). In this analysis, O2 was predicted to be involved in more that 103metabolic reactions not found in anaerobes ([4](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib4), [5](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib5)). O2 is involved in a large number of biosynthetic pathways. Aerobes appear to have adopted O2-dependent mechanisms for synthesis of monounsaturated fatty acids, tyrosine, and nicotinic acid, biomolecules that are also found in more archaic anaerobes; and in a number of macromolecules that carry out more specialized cell functions found exclusively in aerobic metazoans ([16](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib16)). The O2-dependent synthesis of sterols and polyunsaturated fatty acids ([16](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib16)), key components of cell membranes, may have allowed for the biogenesis of intracellular organelles essential for cellular compartmentalization. O2 is also required for a number of biosynthetic reactions for specialized cell functions, such as formation of the connective tissue proteins, hydroxyproline and hydroxylysine ([17](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib17), [18](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib18)), synthesis of the visual pigment, retinal from β-carotene ([19](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib19)), and histone demethylation reactions that regulate chromatin remodeling ([20](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib20)).

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/)

## ROS GENERATION FROM O2 METABOLISM: A DOUBLE-EDGED SWORD

Although O2-dependent biosynthetic reactions and aerobic respiration have significant advantages, the use of O2 in these biological processes represents a double-edged sword. The generation of ROS, either as by-products of O2 metabolism (unintended) or by specialized enzymes (intended), has the potential to cause damage to cellular macromolecules such as proteins, lipid, and DNA. ROS that are capable of such damage include, but are not limited to, superoxide anion (O2·−), hydrogen peroxide (H2O2), and hydroxyl radical (OH·). To counteract toxicity from ROS, all aerobic species possess conserved cellular defense strategies such as that afforded by antioxidant enzymes (e.g., superoxide dismutase, catalase, peroxiredoxins, and glutathione peroxidase) ([21](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib21)). A relative increase in ROS production over antioxidant capacity is often referred to as a state of “oxidative stress” and is implicated in aging and age-associated diseases ([22](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib22), [23](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib23)). A causal role of ROS in these processes is not incontrovertible; nevertheless, the oxidative stress theory of aging remains as viable as any other to explain this complex phenomenon ([24](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib24)). ROS may contribute to age-associated pathologies by their cumulative injurious effects on cells/tissues in an indiscriminate and stochastic manner ([Figure 2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig2/)).

[](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig2/)

[**Figure 2.**](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig2/)

The “oxygen paradox” of fitness/survival during early life of complex metazoans followed by aging and age-associated diseases in later life. The unique biochemical properties of O2 and ROS were exploited and selected during the evolution **...**

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/)

## ROS IN CELLULAR PHYSIOLOGY: MORE THAN MEDIATORS OF CELLULAR INJURY

In addition to its recognized toxic effects, the concept that ROS serve “useful purposes” in normal physiologic processes has gained significant attention in recent years. An example of such a role is the ROS-generating NADPH oxidase (NOX) enzyme, gp91phox (NOX2), which serves host defense against invading microbes ([25](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib25)). In addition, a role for ROS in the transmission of biochemical signals from cell surface receptor–ligand interactions has been increasingly recognized ([26](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib26), [27](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib27)). The precise mechanisms of signal transduction are not known; however, one plausible and well-studied mechanism involves the reversible oxidization of cysteine residues on protein tyrosine phosphatases ([28](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib28), [29](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib29)). In addition to cellular signaling, there are a number of diverse biological contexts in which extracellular H2O2, via peroxidase-catalyzed reactions, mediates tyrosine crosslinking of extracellular matrix (ECM) proteins; examples include the pathogen-evoked hypersensitivity response to restrict spread of pathogens in plants ([30](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib30)), protection of the freshly fertilized egg from polyspermy in sea urchins ([31](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib31), [32](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib32)), stabilization of cuticular extracellular matrix (ECM) in Caenorhabditis elegans ([33](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib33)), and the conferring of “resilient” mechanical properties to resilin found in joints and tendons of insects ([34](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib34)). In mammals, the biosynthesis of thyroxine involves the activity of an H2O2-generating enzyme, a member of the NOX/DUOX gene family ([35](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib35)). The ability of the pro-fibrotic cytokine, transforming growth factor-β1 (TGF-β1), to induce crosslinking of (myo)fibroblast-derived extracellular matrix proteins is dependent on H2O2 in the presence of an extracellular heme peroxidase ([36](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib36)); the specific mammalian peroxidase(s) that mediate such reactions in physiologic/pathophysiologic contexts in vivo requires further study.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/)

## EVOLUTION OF THE ROS-GENERATING NOX GENE FAMILY

Just as the unique chemical/thermodynamic properties of O2 were harnessed for aerobic respiration and biosynthesis during biological evolution, it appears that the chemistry and reactivity of ROS may have also been adopted for purposes of cell signaling/regulation ([Figure 2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig2/)). This is best exemplified by the NOX enzymes, whose primary function is the regulated and compartmentalized generation of ROS ([37](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib37)). Intriguingly, the molecular evolution of NOX family enzymes appears to have increased in number and diversity with increasing complexity during metazoan evolution ([38](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib38), [39](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib39)). NOX enzymes are expressed in all multicellular eukaryotes, including fungi, plants, and animals, but not in prokaryotes ([39](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib39)). Most mammalian species, in particular humans, express seven NOX homologs (NOX1-5 and DUOX1-2), while C. elegansand Drosophila melanogaster each express two members of this gene family ([39](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib39), [40](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib40)). The diversification of NOX gene family with metazoan evolution suggests adaptive roles for these ROS-generating enzymes in more specialized organismal functions. For example, the newest member of this family, NOX3, is found in reptiles, birds, and mammals ([39](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib39)); it is highly expressed in the inner ear, and is required for vestibular sensory function and for perception of gravitational motion and balance ([41](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib41)). Such specialized functions may have been essential (or, at least beneficial) to the adaptation of these species to land. NOX4 appears to be present in all chordates, but not in other metazoans ([39](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib39)). NOX4 is required for the differentiation and activation of myofibroblasts ([42](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib42), [43](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib43)), key cellular mediators of wound repair responses and fibrosis. This raises the possibility that NOX4 may have emerged as an early adaptation of chordates to tissue injury and host repair responses ([Figure 2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig2/)).

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/)

## NOX ENZYMES AND ANTAGONISTIC PLEIOTROPY

The use of O2 and ROS in normal physiologic processes presents an apparent paradox for the fitness and survival of mammalian species ([44](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib44)). While the use of O2 and generation of ROS have “useful,” physiologic purposes, they may also play a role in aging and age-associated degenerative diseases. One explanation for this paradox is the concept of antagonistic pleiotropy, which posits that genes selected because of their beneficial effects during early/reproductive life may also mediate deleterious effects in later life, a theory that was originally proposed to explain cellular senescence ([45](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib45), [46](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/#bib46)). NOX2, an enzyme that was present in early multicellular eukaryotes as a critical component of the innate immune response and conserved in mammals, may also play a role in chronic inflammatory conditions in mature adults. The more recently identified NOX4 homolog and its function in myofibroblast differentiation/activation supports the possibility that this gene may also function in an “antagonistically pleiotropic” manner. While NOX4 and myofibroblasts may regulate wound repair responses in early life, this regulatory pathway may prove to be detrimental by promoting tissue fibrosis and organ dysfunction in later life ([Figure 2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/figure/fig2/)). Myofibroblasts are key mediators of fibrogenesis in a number of human fibrotic disorders, including idiopathic pulmonary fibrosis, a disease typically associated with aging. One wonders if aging and age-associated diseases are the “price we pay” for the evolutionary conservation and diversification of O2/ROS-using metabolic pathways to produce more energy-efficient, larger, and more complex species. On the other hand, life on our planet would look very different without having had the availability of O2 in our biosphere. An understanding of the evolutionary selection and the (difficult) choices made during evolution of complex metazoans has the potential to provide novel insights into disease pathogenesis and innovative strategies for treatment of age-associated human maladies.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/)

## Acknowledgments

The author thanks members of his laboratory, and colleagues at the University of Michigan, and many others outside this institution for stimulating discussions on topics related to the content of this article.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720141/)

## Notes

This work was supported in part by National Institutes of Health grants R01 HL67967 and P50 HL74024 to V.J.T.

Originally Published in Press as DOI: 10.1165/rcmb.2008-0360PS on October 31, 2008

**Conflict of Interest Statement:** The author does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. References

1. Falkowski PG, Katz ME, Milligan AJ, Fennel K, Cramer BS, Aubry MP, Berner RA, Novacek MJ, Zapol WM. The rise of oxygen over the past 205 million years and the evolution of large placental mammals.Science 2005;309:2202–2204. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/16195457)]

2. Acquisti C, Kleffe J, Collins S. Oxygen content of transmembrane proteins over macroevolutionary time scales. Nature 2007;445:47–52. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/17183269)]

3. Bekker A, Holland HD, Wang PL, Rumble D III, Stein HJ, Hannah JL, Coetzee LL, Beukes NJ. Dating the rise of atmospheric oxygen. Nature 2004;427:117–120. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/14712267)]

4. Raymond J, Segre D. The effect of oxygen on biochemical networks and the evolution of complex life.Science 2006;311:1764–1767. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/16556842)]

5. Falkowski PG. Evolution: tracing oxygen's imprint on earth's metabolic evolution. Science2006;311:1724–1725. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/16556831)]

6. Catling DC, Glein CR, Zahnle KJ, McKay CP. Why O2 is required by complex life on habitable planets and the concept of planetary “oxygenation time”. Astrobiology 2005;5:415–438. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/15941384)]

7. Rosing MT. 13c-depleted carbon microparticles in >3700-ma sea-floor sedimentary rocks from west Greenland. Science 1999;283:674–676. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/9924024)]

8. Brocks JJ, Logan GA, Buick R, Summons RE. Archean molecular fossils and the early rise of eukaryotes.Science 1999;285:1033–1036. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/10446042)]

9. Hayes JM, Waldbauer JR. The carbon cycle and associated redox processes through time. Philos Trans R Soc Lond B Biol Sci 2006;361:931–950. [[PMC free article](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1578725/)] [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/16754608)]

10. Kump LR, Barley ME. Increased subaerial volcanism and the rise of atmospheric oxygen 2.5 billion years ago. Nature 2007;448:1033–1036. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/17728754)]

11. Hedges SB, Blair JE, Venturi ML, Shoe JL. A molecular timescale of eukaryote evolution and the rise of complex multicellular life. BMC Evol Biol 2004;4:2. [[PMC free article](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC341452/)] [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/15005799)]

12. Bonner JT. On the origin of differentiation. J Biosci 2003;28:523–528. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/12799498)]

13. Kennedy M, Droser M, Mayer LM, Pevear D, Mrofka D. Late precambrian oxygenation: inception of the clay mineral factory. Science 2006;311:1446–1449. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/16456036)]

14. Benton MJ. Diversification and extinction in the history of life. Science 1995;268:52–58. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/7701342)]

15. Berner RA, Vandenbrooks JM, Ward PD. Evolution: oxygen and evolution. Science 2007;316:557–558.[[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/17463279)]

16. Goldfine H. The evolution of oxygen as a biosynthetic reagent. J Gen Physiol 1965;49:253–274.[[PMC free article](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2195466/)] [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/5859924)]

17. Fujimoto D, Tamiya N. Incorporation of O from air into hydroxyproline by chick embryo. Biochem J1962;84:333–335. [[PMC free article](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1243670/)] [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/16748956)]

18. Towe KM. Oxygen-collagen priority and the early metazoan fossil record. Proc Natl Acad Sci USA1970;65:781–788. [[PMC free article](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC282983/)] [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/5266150)]

19. Sumper M, Reitmeier H, Oesterhelt D. Biosynthesis of the purple membrane of halobacteria. Angew Chem Int Ed Engl 1976;15:187–194. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/822754)]

20. Forneris F, Binda C, Battaglioli E, Mattevi A. Lsd1: oxidative chemistry for multifaceted functions in chromatin regulation. Trends Biochem Sci 2008;33:181–189. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/18343668)]

21. McCord JM, Fridovich I. Superoxide dismutase: an enzymic function for erythrocuprein (hemocuprein).J Biol Chem 1969;244:6049–6055. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/5389100)]

22. Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. Cell 2005;120:483–495. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/15734681)]

23. Finkel T. Radical medicine: treating ageing to cure disease. Nat Rev Mol Cell Biol 2005;6:971–976.[[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/16227974)]

24. Kirkwood TB. Understanding the odd science of aging. Cell 2005;120:437–447. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/15734677)]

25. Nauseef WM. NOX enzymes in immune cells. Semin Immunopathol 2008;30:195–208. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/18449540)]

26. Thannickal VJ, Fanburg BL. Reactive oxygen species in cell signaling. Am J Physiol Lung Cell Mol Physiol 2000;279:L1005–L1028. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/11076791)]

27. Lambeth JD. NOX enzymes and the biology of reactive oxygen. Nat Rev Immunol 2004;4:181–189.[[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/15039755)]

28. Rhee SG, Bae YS, Lee SR, Kwon J. Hydrogen peroxide: a key messenger that modulates protein phosphorylation through cysteine oxidation. Sci STKE 2000;2000:PE1. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/11752613)]

29. Xu D, Rovira II, Finkel T. Oxidants painting the cysteine chapel: redox regulation of PTPS. Dev Cell2002;2:251–252. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/11879627)]

30. Levine A, Tenhaken R, Dixon R, Lamb C. H2O2 from the oxidative burst orchestrates the plant hypersensitive disease resistance response. Cell 1994;79:583–593. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/7954825)]

31. Shapiro BM. The control of oxidant stress at fertilization. Science 1991;252:533–536. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/1850548)]

32. Wong JL, Wessel GM. Free-radical crosslinking of specific proteins alters the function of the egg extracellular matrix at fertilization. Development 2008;135:431–440. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/18094022)]

33. Edens WA, Sharling L, Cheng G, Shapira R, Kinkade JM, Lee T, Edens HA, Tang X, Sullards C, Flaherty DB, et al. Tyrosine cross-linking of extracellular matrix is catalyzed by duox, a multidomain oxidase/peroxidase with homology to the phagocyte oxidase subunit gp91phox. J Cell Biol 2001;154:879–891. [[PMC free article](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2196470/)] [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/11514595)]

34. Elvin CM, Carr AG, Huson MG, Maxwell JM, Pearson RD, Vuocolo T, Liyou NE, Wong DC, Merritt DJ, Dixon NE. Synthesis and properties of crosslinked recombinant pro-resilin. Nature 2005;437:999–1002.[[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/16222249)]

35. Milenkovic M, De Deken X, Jin L, De Felice M, Di Lauro R, Dumont JE, Corvilain B, Miot F. Duox expression and related H2O2 measurement in mouse thyroid: Onset in embryonic development and regulation by tsh in adult. J Endocrinol 2007;192:615–626. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/17332529)]

36. Larios JM, Budhiraja R, Fanburg BL, Thannickal VJ. Oxidative protein cross-linking reactions involving l-tyrosine in transforming growth factor-beta1-stimulated fibroblasts. J Biol Chem 2001;276:17437–17441.[[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/11279068)]

37. Bedard K, Krause KH. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol Rev 2007;87:245–313. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/17237347)]

38. Kawahara T, Quinn MT, Lambeth JD. Molecular evolution of the reactive oxygen-generating NADPH oxidase (NOX/DUOX) family of enzymes. BMC Evol Biol 2007;7:109. [[PMC free article](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1940245/)] [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/17612411)]

39. Sumimoto H. Structure, regulation and evolution of NOX-family NADPH oxidases that produce reactive oxygen species. FEBS J 2008;275:3249–3277. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/18513324)]

40. Bedard K, Lardy B, Krause KH. NOX family NADPH oxidases: not just in mammals. Biochimie2007;89:1107–1112. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/17400358)]

41. Paffenholz R, Bergstrom RA, Pasutto F, Wabnitz P, Munroe RJ, Jagla W, Heinzmann U, Marquardt A, Bareiss A, Laufs J, et al. Vestibular defects in head-tilt mice result from mutations in Nox3, encoding an NADPH oxidase. Genes Dev 2004;18:486–491. [[PMC free article](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC374230/)] [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/15014044)]

42. Thannickal VJ, Fanburg BL. Activation of an H2O2-generating NADH oxidase in human lung fibroblasts by transforming growth factor beta 1. J Biol Chem 1995;270:30334–30338. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/8530457)]

43. Cucoranu I, Clempus R, Dikalova A, Phelan PJ, Ariyan S, Dikalov S, Sorescu D. NAD(P)H oxidase 4 mediates transforming growth factor-beta1-induced differentiation of cardiac fibroblasts into myofibroblasts.Circ Res 2005;97:900–907. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/16179589)]

44. Lambeth JD. Nox enzymes, ROS, and chronic disease: an example of antagonistic pleiotropy. Free Radic Biol Med 2007;43:332–347. [[PMC free article](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2013737/)] [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/17602948)]

45. Williams GC. Pleiotropy, natural selection, and the evolution of senescence. Evolution Int J Org Evolution 1957;11:398–411.

46. Kirkwood TB, Rose MR. Evolution of senescence: late survival sacrificed for reproduction. Philos Trans R Soc Lond B Biol Sci 1991;332:15–24. [[PubMed](http://www.ncbi.nlm.nih.gov/pubmed/1677205)]